Phase I Oncology Studies

Summary: This program of research, comprised of both conceptual and empirical studies, seeks to better understand the ethical issues involved in Phase I oncology clinical trials, including exploration of issues related to research design, motivations and understanding of Phase I participants, vulnerability of participants, informed consent and factors that promote misunderstanding, and appropriate safeguards.

Section: Human Subjects Research- Unit on Clinical Research

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Background: The paradigmatic objective of the Phase I oncology trial is to determine the maximal safe dose of an investigational agent that may never have been previously tested in humans. This usually involves stepwise dose-escalation of an investigational agent in small cohorts of participants who have advanced disease and have exhausted standard therapeutic options. Because the agents are new and dose escalation begins with a deliberately low dose, the prospect of direct clinical benefit to patient-subjects may be extremely low, while the risks may be significant. Meta-analyses place the average response rate for Phase I oncology trials at less than 6 percent and the toxic death rate at approximately 0.5 percent. However, the most recent meta-analysis of response rate, toxic side effects, or research related deaths in Phase I oncology trials was done in the 1980s, and there are other reasons that the data on risk and benefit in Phase I trials deserve a closer look.

Traditionally response rate has been calculated by measuring change in tumor burden. While still an appropriate marker for many cancer interventions, response to novel agents such as immunomodulators may be more appropriately measured by different endpoints. The association of response as measured by various surrogate endpoints and meaningful clinical change or increased survival needs more attention. Dramatic examples of responses to certain drugs being tested in Phase I trials (such as Gleevac for chronic myeloid leukemia) , and the fact that less than a third of Phase I trials in 1999 were classic early chemotherapy trials suggest the need for a re-evaluation of the response rate in Phase I oncology studies. Furthermore, and perhaps as or more important from an ethical perspective, other possible benefits of participation in Phase I trials such as psychological benefits or benefit to patients' quality of life have not been well studied and may be underestimated.

Participants of Phase I oncology studies are often perceived to be 'vulnerable' as they generally are well advanced in their disease and have few therapeutic options. Ethicists and others worry about these participants' ability to make voluntary and informed choices about research participation, in the face of severely limited options and a reduced life expectancy. Although some have questioned the ethics of involving ill patients in these studies at all, most ethical commentary written about phase I cancer trials focuses on the alleged inadequacies of informed consent from this 'vulnerable' group. Concern about informed consent is based on an underlying assumption that patients do not adequately understand the nature or purpose of research and tend to overestimate potential benefits for themselves from participation in Phase I trials. According to one commentator, 90 percent of patient-subjects' misunderstandings about Phase I trials "reveal problems with informed consent." Described as desperate and vulnerable, participants are assumed susceptible to being misled by investigators or by the written information in consent documents and/or are unable to clearly understand what they are being told. The implication is that *if* patients really understood the purpose of the research and the low chance of therapeutic benefit, they would not participate in Phase I trials.

These concerns have provided a basis for some important empirical work on informed consent in Phase I trials. The few empirical studies that have been conducted with Phase I oncology participants suggest that, in fact, many subjects do *not* understand critical aspects of the research. Despite the estimated low prospect of clinical benefit, studies have found that most participating patients are motivated by hopes for stabilization, tumor shrinkage, clinical improvement, or even cure of their diseases. For instance, Daugherty and colleagues found that almost ¾ of patients (73%) enrolling in phase I studies were motivated by the possibility of an anticancer response. While 93% of the patients reported they understood most or all of the information given to them about the trial in which they had agreed to participate, only 33% of the participants were able to state the purpose of phase I studies as dose-finding studies. Studies like Daugherty's have led to the conclusion that "unrealistic expectations and false hope in patients who consider phase I studies may need to be addressed in the informed-consent process". Others have worried that patients with terminal cancer asked to participate in research are vulnerable to a therapeutic misconception, i.e. a

misconception that what is being offered to them is clinical care and designed specifically to benefit them. Consent forms themselves are thought to be part of the problem, as they are alleged to distort information to increase enrollment, make the tested agents "sound like the cure for cancer," and "may actually be interfering with what might otherwise be an ethically appropriate informed consent process." Thus, much research and effort has been directed towards improving consent forms and more generally the informed consent process in Phase I oncology research.

However, data on informed consent from patients with advanced cancer who enroll in phase I cancer studies are limited in several ways. Studies published to date have all been conducted at a single institution with a small numbers of patient using methodologies that have not been rigorously tested. Perhaps more importantly, these studies may be limited in their conceptual aims. Published studies have addressed patient comprehension of disclosed information without systematically considering the possibly unique perspectives brought by ill patients and how they might view the opportunity to participate in research. None of the studies have considered the possibility that subjects may not recall particular informational aspects of the research study because this information was not important to their decision about participation.

Furthermore, existing studies have not considered, and therefore little is known about, the complex psychological outlook of those with a terminal illness; the extent to which personality type affects decision making; the role hope plays in the decision making of patients with a terminal illness; the perhaps unique and likely complex risk/benefit calculation patients undertake; and their information seeking behavior when making decisions about research participation. Yoder et al. in their evaluation of phase I patients said that "optimism or hope may be integral to the psychological framework of patients choosing to enter phase I trials or … a more optimistic personality type [may be] more prone to volunteer for investigational therapy." Zimmer describes distinct personality traits and mental characteristics that influenced his perspective as a participant in phase I studies.

A related problem, and one that certainly goes beyond decisions made by participants in Phase I trials, is understanding what can compromise or 'unduly' influence a person's decision about research participation. Encouragement by family members, health care providers and others may be important for people making difficult decisions, but excessive encouragement could actually become pressure that patients find hard to resist. Even less well understood is the pressure that people may feel because of the circumstance of their illness, and the extent to which circumstances affects one's ability to make choices.

Objectives:

1) To critically evaluate ethical concerns associated with Phase I oncology studies.

2) To analyze and describe the substantive content of Phase I oncology trial consent forms, especially the way that research purpose, risks, benefits, and alternatives are described.
3) To distinguish different types of possible misunderstanding in research.
4) To evaluate and describe the personality characteristics/profile of people who agree to participate in Phase I oncology research.
5) To explore the psychological outlook and perspectives on acceptable risks and benefits of people who agree to participate in Phase I oncology research
6) To describe the variety of studies that make up Phase I oncology research and seek a more nuanced understanding of the prospect of direct benefit and serious side effects from participation.
7) To explore other potential risks (e.g. cost) and benefits (e.g. psychological benefit) associated with participation in Phase I oncology research

Methodology: Initially, we conducted a thorough literature search on Phase I oncology research and discussion of the ethical issues, collecting articles, research reports, and commentary on the subject. The arguments, methodologies, and data from these articles were reviewed, analyzed and discussed among members of the Department in various settings, informally, at research team meetings, and at works-in-progress meetings. We also discussed these issues with investigators and other research team members both in the NIH intramural program and outside the NIH. Conceptually, our interests have focused primarily on exploring concepts of vulnerability and exploitation with respect to participants of Phase I oncology research, and the ability of desperately ill people to make voluntary informed decisions. We also undertook a critical review of ethical concerns in Phase I trials.

Empirically, we have several projects related to Phase I oncology studies. One study sought to analyze the substantive content of consent forms for Phase I oncology studies in the U.S. We evaluated the written description of research purpose, risks, benefits and alternatives in 272 consent forms approved in 1999, collected from 46 NCI designated Cancer Centers and 8 pharmaceutical companies. A second project seeks to describe the complex psychological attitudes and make-up of 250 Phase I participants at 5 cancer centers in the U.S as it relates to their understanding and decision making about participation in research through detailed in-person interviews and a formal standard personality assessment. A third project will utilize existing databases to calculate response rates and toxicities for Phase I trials by type of trial, type of response, type of tumor, type of patient (ie adult or child), and other parameters.

Results

Drs Agrawal and Emanuel examined two fundamental ethical challenges in Phase I oncology research: the risk/benefit ratio and informed consent. Noting that Phase I cancer research is critical to finding therapeutic interventions for cancer, they argue that

many of the ethical concerns about Phase I research are based on limited data and an inadequate appreciation of what concerns patients, and may therefore be misplaced. More detailed and current information about response rates as well as other types of benefits and risks from Phase I trials, an appreciation of how the risk/benefit profile of Phase I studies compares to the risk/benefit profile of approved and standard therapeutic options for cancer, and more systematic inclusion of the views of patients, would inform our analysis of Phase I risks and benefits. They also argue for more rigorous study of what patients perceive as the value of participation in Phase I research (appreciation instead of just comprehension) and how they make risk benefit trade-offs. In another paper, it is argued that there is no categorical reason to believe that people at the end of their lives cannot make informed and voluntary decisions. Being faced with poor or limited options does not equate with not being able to choose between options. We argue that rather than assume that participants are unable to make voluntary decisions, our attentions should be focused on avoiding exploitation by being sure that the risk/benefit profile of the proposed research is justified and fair, and that safeguards are established for possible vulnerability created by dependence on institutions or particular relationships. In yet another paper, we argue that misunderstanding by participants of clinical research can be differentiated into several types: a therapeutic misconception (a misconception about the nature and purpose of research), a therapeutic misestimation (an overestimation of the potential for benefit from the research), and therapeutic optimism (hope for the most positive outcome). Each type of misunderstanding has different ethical implications and calls for a different approach to correcting the misunderstanding.

In the study of Phase I oncology consent forms, we discovered that the majority of consent forms from studies conducted in 1999 explicitly described the purpose of the research, did not overpromise benefit, and emphasized the seriousness and unpredictability of risk . Although improvements could be made in the written forms, such as avoiding the unmodified use of the word “treatment,” written consent forms are unlikely to be the major source of misunderstanding among Phase I oncology trial participants. Surprisingly, we also found that of 272 consent forms for Phase I trials, only 29% were for ‘classic’ dose-escalating trials of novel chemotherapeutic agents. The rest included novel combinations of drugs already tested or approved, or evaluations of antiangiogenesis agents, immunologic agents, vaccines, and other interventions. This variety argues for a more nuanced approach to understanding and describing the risks, benefits, and alternatives of Phase I studies.

The project evaluating the psychological profile and personality traits of Phase I participants began in late 2002 at 5 sites: NIH, MD Anderson, Northwestern, Fox Chase Cancer Center, and the Institute for Drug Development and Cancer Therapy in San Antonio. Pilot studies in two separate institutions led to important revisions in the questionnaire. The study is likely to take another year to complete.

Future Directions:

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We have begun a project, employing analysis of large databases available through CTEP at NCI, that seeks to update and refine the estimates for response (complete and partial) and toxic side effects and deaths for both adult and pediatric participants in Phase I oncology trials. We are planning to continue to explore the notions of vulnerability, undue influence, and the influence of dependent relationships on decisions about research. We are also examining the extent to which patients participating in Phase I oncology studies experience out of pocket costs associated with their participation, arguing that since they are primarily contributing to the public good through their participation, costs of research participation and compensation for research injury should be covered by other mechanisms.

Publications:

Agrawal, M Voluntariness in Patients at the End of Live, *Journal of Pain and Symptom Management* , (under review)

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